First-line therapies in inflammatory bowel disease

Girardin, Marc ; Manz, Michael ; Manser, Christine ; Biedermann, Luc ; Wanner, Roger ; Frei, Pascal ; Safroneeva, Ekaterina ; Mottet, Christian ; Rogler, Gerhard ; Schoepfer, Alain M

Abstract: BACKGROUND AND AIMS: Medical therapy of inflammatory bowel disease (IBD) is becoming more complex, given the increasing choice of drugs to treat Crohn's disease (CD) and ulcerative colitis (UC). We aimed to summarize the current guidelines for first-line treatments in IBD. METHODS: An extensive literature search with focus on the guidelines of the European Crohn's and Colitis Organisation for the diagnosis and treatment of CD and UC was performed. First-line treatments were defined as the following drug categories: 5-aminosalicylates, budesonide, systemic steroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab and certolizumab pegol. The following drug categories were not included: cyclosporine and tacrolimus (not yet approved by Swissmedic for IBD treatment). RESULTS: Treatment recommendations for the following clinically frequent situations are presented according to disease severity: ileocecal CD, colonic CD, proximal small bowel CD and perianal CD. For UC the following situations are presented: ulcerative proctitis, left-sided colitis and pancolitis. CONCLUSIONS: We provide a summary on the use of first-line therapies for clinically frequent situations in patients with CD and UC.

DOI: https://doi.org/10.1159/000341951

First line therapies in Inflammatory Bowel Disease

Marc Girardin, MD[1], Michael Manz[2], Christine Manser[3], Luc Biedermann[3], Roger, Wanner[3], Pascal Frei[3], Christain Mottet[4,5], Gerhard Rogler[3], Alain M. Schoepfer, MD[4]

[1]Division of Gastroenterology and Hepatology, University Hospital Geneva, Geneva, Switzerland

[2]Division of Gastroenterology and Hepatology, Claraspital, Basel, Switzerland

[3]Division of Gastroenterology & Hepatology, University Hospital of Zürich, Zürich, Switzerland

[4]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois / CHUV, Lausanne, Switzerland

[5]Division of Gastroenterology and Hepatology, Hôpital de Neuchatel, Switzerland

Address for correspondence and reprints:

Marc Girardin, MD

Division of Gastroenterology and Hepatology

University Hospital Geneva

4 place Gabrielle-Perret Gentil

1211 Geneve 14

Tel +41223729340

Fax +41223829021

Running head: First line therapies in IBD

Key words: inflammatory bowel disease, therapy, steroids, aminosalicylates, Crohn, ulcerative colitis

Conflict of interest: the authors declare no conflict of interest

Writing assistance: none

Grant support: This research was supported by grants from the Swiss National Science Foundation (SNF) to AS (Grant No. 32003B_135665/1), and the Swiss IBD Cohort (Grant No. 3347CO-108792).

Statistics: 1810 words (without abstract), 1 table, 30 references

ABSTRACT

Background and Aims: Medical therapy of inflammatory bowel diseases (IBD) is becoming more complex given the increasing choice of drugs to treat Crohn's disease (CD) and ulcerative colitis (UC). We aimed to summarize the current guidelines for first line treatments in IBD.

Methods: An extensive literature search with focus on the guidelines of the European Crohn's and Colitis Organisation (ECCO) for diagnosis and treatment of CD and UC was performed. First line treatments were defined as the following drug categories: 5-aminosalicylates (5-ASA), budesonide, systemic steroids, Azathioprine, 6-mercaptopurine, Methotrexate, Infliximab, Adalimumab, and Certolizumab pegol. The following drug categories are not included: cyclosporine, tacrolimus, drugs not yet approved by Swissmedic for IBD treatment.

Results: Treatment recommendations for the following clinically frequent situations are presented according to disease severity: ileocecal CD, colonic CD, proximal small bowel CD, and perianal CD. For UC the following situations are presented: ulcerative proctitis, left-sided colitis, pancolitis.

Conclusions: We provide a summary on the use of first line therapies for clinically frequent situations in patients with CD and UC.

171 words

INTRODUCTION

Inflammatory bowel diseases (IBD) are characterized by the presenc of chronic, non-infectious inflammatory processes of the bowel of unkown origin. Current evidence suggests that, based on several genetic abnormalities, a dysbalanced mucosal immune system reacts in an uncontrolled way to luminal antigens.[1] The diagnosis of IBD is made based on a mixed picture consisting of symptoms, endoscopic findings, histology, radiologic exams, and laboratory markers, once other causes for inflammatory bowel diseases, such as infections, have been ruled out. The two main diseases are Crohn's disease (CD) and Ulcerative colitis (UC). CD is characterized by a transmural inflammation classically involving the terminal ileum and the proximal colon. One third of the patients present only a colonic involvement and one other third have a more diffuse disease involving the small bowel as well as the stomach or the esophagus. Characteristic for CD is the transmural inflammation that may lead to structural complications such as stenoses, internal or external and also perianal fistulas. Inflammation in UC is typically limited to the colon and histologically to the mucoas (and submucosa). Depending on the extent, an ulcerative proctitis is discriminated from a left-sided colitis and a pancolitis. Both CD and UC can be complicated by the appearance of extra-intestinal manifestations (due to antigen cross-reactivity) such as inflammation of the eyes (uveitis, conjunctivitis), joints (arthritis), skin (pyoderma gangrenosum, erythema nodosum) or liver (primary sclerosing cholangitis).[2]

The choice of medical management for IBD patients depends on activity, location, extension, and potential involvement of other organs. The assessment of these items allows a tailored therapeutic approach. Treatment in IBD is divided into an induction phase in which a response or remission is aspired and the maintenance treatment in

which the response or remission should be carried on further. The following chapters will review the first line treatment choices for CD and UC, including induction and maintenance therapies. The following drug categories are summarized under first line therapies: aminosalicylates (5-ASA), budesonide, systemic steroids (prednisone and derivates), Azathioprine, 6-mercaptopurine, Methotrexate, Infliximab, Adalimumab, and Certolizumab pegol. The following "second-line" treatments will not be discussed: cyclosporine, tacrolimus.

CROHN'S DISEASE

Ileo-cecal CD

The ileo-cecal location represents the typical CD presentation. In mild to moderately active ileo-cecal CD (CDAI up to 300 points), Budesonide 9 mg per day is the best choice to induce clinical remission. Budesonide has been shown its superiority to placebo and to mesalazine and has fewer side effects than systemic corticosteroids.[3] However, in one recent study, the authors found that mesalazine 4.5 g per day was comparably efficient to budesonide to induce remission (69.5% for budesonide compared to 62.1% for mesalazine).[4] A CDAI drop of 100 points was observed in 89% of budesonide-treated patients compared to 79% of mesalazine-treated patients.[4]

In case of severe clinical activity (defined as CDA > 300 points) systemic corticosteroids (either prednisolone per os or intervenous hydrocortisone) should be applied.[3] In CD patients with steroid-refractory or steroid-dependent disease, an early introduction of anti-TNF therapies can be beneficial. The step-up-vs top-down study showed that even treatment naïve patients could benefit from this strategy.[5]

Surgery is not the primary focus of our review, it should considered in case of ileo-cecal CD that is resistant to medical therapy.

Maintenance therapy is usually indicated after induction of response and/or remission by corticosteroids as these drugs are not effective in maintaining the response or remission, respectively, and they are furthermore associated with adverse treatment effects such as osteoporosis or increased infection risk.[6]

Azathioprine (2–2.5 mg/kg/day) is the most commonly used drug for this situation and has proven efficacy for maintaining CD in remission and also for having steroid-sparing effects.[7] Methotrexate at weekly doses of 15 mg i.m. has also demonstrated efficacy in maintaining CD in remission.[8,9]

Colonic CD

Active colonic CD should be treated with systemic steroids for induction of response and remission. Budesonide is not effective for colonic CD due to its limited action on the proximal colon. Azathioprine, 6-mercaptopurine, or methotrexate can be used as steroid sparing agents for maintaining the medically induced remission.[7-9] In relapsing disease, Anti-TNF drugs (Infliximab, Adalimumab or Certolizumab pegol) can be applied for induction and maintenance of remission with or without a combination by an immunomodulator.[10] The SONIC trial evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe CD who were naïve to previous treatments with either an immunomodulator (Azathioprine or 6-mercaptopurine or methotreaxate) or biologic therapy.[11] Of the patients receiving combination therapy, 56.6% were in corticosteroid-free clinical remission at week 26, compared with 44.4% of patients receiving infliximab monotherapy ($p = 0.02$) and 30.0% of patients receiving azathioprine monotherapy ($p < 0.001$ for the comparison with combination therapy

and p = 0.006 for the comparison with infliximab). Similar numerical trends were found at week 50. If combination therapy is associated with similar benefits in CD populations no longer naïve to immunomodulators and / or anti-TNF drugs remains to be investigated.

Extensive small bowel CD

Extensive small bowel CD is defined as disease affecting > 100 cm of small bowel and therefore carrying the risk of nutritional deficiencies.[12] Treatment of extensive intestinal CD is equivalent to other localization of CD. Systemic steroids should be used to induce clinical remission. The early introduction of immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) is recommended given their steroid-sparing effects in the long-term run.[12] The early introduction of anti-TNF therapy should also be considered especially for the population with clinical indicators of poor prognosis such as young age at diagnosis, initial need for steroid therapy, and the presence of perianal disease.[13]

Perianal CD

Perianal fistulae in CD are classified into simple and complex fistulae.[14] Before deciding on specific treatment for perianal CD, a pelvic MRI should be performed for assessment of disease location and severity.[15] The imaging will also detect the presence of perianal abscesses which should be drained urgently. In addition, a procto-sigmoidoscopy should be performed as the presence of ongoing rectosigmoid inflammation influences the treatment success.[15] In fact, evidence suggests that fistula treatment is not successful without treatment of the underlying active disease.[16] Only symptomatic perianal fistulae should be treated.[15]

The treatment of the fistulizing CD itself is based on antibiotics, immunomodulators (Azathioprine or 6-mercaptopourine or methotrexate) or Anti-TNF drugs.

Metronidazole and/or ciprofloxacin have been studied only in small patient series. They are effective in reducing symptoms but less in inducing fistula healing.[17] There exist no randomized controlled trials having evaluated the efficacy of azathioprine and mercaptopurine on the closure of perianal fistulae as primary end point in CD patients. A meta-analysis of five randomized controlled trials where closure of perianal fistulae was assessed as secondary end point favors the use of azathioprine and 6-mercaptopurine for induction and maintenance of perianal fistula closure.[18]

Infliximab was the first anti-TNF agent to demonstrate in a randomized controlled trial effectiveness in inducing closure of perianal fistulae and maintaining this response over one year. An induction treatment with 5 mg infliximab/kg at weeks 0, 2, and 6 led to a complete closure (defined as cessation of all drainage on 2 visits 1 month apart) in 17/31 (55%) of patients.[19] In the ACCENT II trial, 33/91 (36%) of patients on infliximab had complete fistula closure at week 54 compared to 19/98 (19%) on placebo ($p = 0.009$).[20]

In the CHARM trial, CD patients treated with adalimumab showed at week 26 a fistula remission of 30% compared to 13% on placebo ($p = 0.04$) and at week 56 a fistula remission of 33% compared to 13% in the placebo group ($p = 0.02$).[21]

The Swiss FACTS survey demonstrated that certolizumab pegol was associated with a perianal fistula closure rate of 36% at week 6 and of 55% closure rate at week 26.[22]

ULCERATIVE COLITIS

Ulcerative proctitis

Active proctitis should first be treated topically. Topical mesalazine (5-ASA) was able to induce remission in active proctitis and distal colitis in 31-80% (median 67%) compared to 7-11% in patients treated with placebo in a meta-analysis evaluating 11 trials with a total of 778 patients.[23] Topical mesalazine proved to be at least twice as effective as topical corticosteroids with regard to symptom improvement (OR 2.42, 95% CI 1.72-3.41), endoscopic improvement (OR 1.89, 95% CI 1.29-2.76), or histologic improvement (OR 2.03, 95% CI 1.28-3.20).[24] Topical mesalazine should be applied with a dosage of 1 gram per day. Combining topical and oral mesalazine is more effective than either alone for colitis < 50cm from the anal verge.[25] In case of insufficient response to topical mesalazine, the combination of these with topical steroids (beclomethasone dipropionate) can be beneficial.[26] Patients failing to improve on a combination of topical mesalazine, oral mesalazine, and topical steroids, should be treated with oral prednisolone.[25]

Left sided colitis

As for distal proctitis, treatment of left sided colitis is based on mesalazine. The combination of oral and topical mesalazine therapy is recommended.[25] A meta-analysis of mesalazine showed a dose-response for clinical improvement from <2.0 g, 2.0-2.9 g, and > 3.0 g daily ($p = 0.002$), but not for remission.[27] Thus, induction of remission of left-sided UC should be performed by prescribing mesalazine at a daily dosage of at least 3 grams. In severe left sided UC as well as in mesalazine-refractory moderate left sided UC, oral steroids (prednisolone) are the treatment of choice for induction therapy. Maintenance of remission can be achieved using mesalazine in lower dosages than used for induction treatment.[28]

Pancolitis

As for the left sided UC, pancolitis should be treated following the same rules, but systemic steroids should be used faster than in left sided colitis depending on the severity. Again the combination of both oral and topical mesalazine is more effective for induction of remission.[29] Steroids should be weaned progressively by 10 mg per week until 20 mg and then by 5 mg per week for the timely recognition of steroid-dependence. In case of steroid dependency, immunomodulators should be started.

In mild to moderate pancolitis, mesalazine can also be used as maintenance therapy.[28] In moderate to severe pancolitis azathioprine proved to be more effective than placebo for maintaining remission.[30] Azathioprine should be started when frequent relapses are observed while the patient is on maintenance therapy with mesalazine or in case of steroid dependence.

Acute severe colitis is a particular condition carrying a substantial risk for colectomy. Intravenous steroids should be started early and their effect should be monitored closely and response should be assessed at 3 to 5 days.[25] If an adequate response is not achieved under iv steroids, second line treatment with Infliximab or cyclosporine should be initiated. Maintenance therapy can be achieved either by continuing Infliximab or with azathioprine that replaces cyclosporine after the acute phase.[25]

CONCLUSIONS

Therapy of CD and UC is based on disease location and disease severity, taking also into account the presence of prognostic factors for a disabling disease course in case of CD. The recommendations for induction therapies are summarized in **Table 1**.

Table 1

Induction therapies for IBD depending on disease location and severity

	Mild activity	**Moderate activity**	**Severe activity**
Crohn's Disease			
Ileo-caecal	Budesonide	Budesonide	Corticosteroids
Colonic	Corticosteroids	Corticosteroids	Corticosteroids Anti-TNF
Extensive small bowel	Corticosteroids Anti-TNF	Corticosteroids Anti-TNF	Corticosteroids Anti-TNF
Perianal	Antibiotics Surgical drainage	Antibiotics Surgical drainage Anti-TNF	Antibiotics Surgical drainage Anti-TNF
Ulcerative Colitis			
Proctitis	Topical aminosalicylates	Topical aminosalicylates	Topical aminosalicylates Topical steroids
Left sided colitis	Topical and oral aminosalicylates	Topical and oral aminosalicylates Corticosteroids	Topical and oral aminosalicylates Corticosteroids
Pancolitis	Topical and oral aminosalicylates Corticosteroids	Topical and oral aminosalicylates Corticosteroids	Topical and oral aminosalicylates Corticosteroids Anti-TNF Cyclosporine

REFERENCES

[1] Scharl M, Rogler G. Inflammatory bowel disease pathogenesis : what is new? Curr Opin Gastroenterol 2012;28:301-309.

[2] Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, Rogler G, Schoepfer AM. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011;106:110-119.

[3] Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008;3:CD000296.

[4] Tromm A, Bunganič I, Tomsová E, Tulassay Z, Lukáš M, Kykal J, Bátovský M, Fixa B, Gabalec L, Safadi R, Kramm HJ, Altorjay I, Löhr H, Koutroubakis I, Bar-Meir S, Stimac D, Schäffeler E, Glasmacher C, Dilger K, Mohrbacher R, Greinwald R; International Budenofalk Study Group. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. Gastroenterology. 2011 Feb; 140(2):425-434.

[5] D'Haens G, Baert F, van Assche G, et al. Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008; 371:660–667.

[6] Toruner M, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929-936.

[7] Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000067.

[8] Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 2000; 342:1627–1632.

[9] Arora S, Katkov W, Cooley J, et al. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebocontrolled trial. Hepatogastroenterology 1999; 46:1724–1729.

[10] Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of anti-tumor necrosis factor agents in Crohn's disease: a meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008; 6:644–653.

[11] Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15; 362(15):1383-1395.

[12] Dignass A, Van Assche G, Lindsay JO, Lemann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollon F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SPL. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010;4:28-62.

[13] Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. Gastroenterology 2006;130:650-656.

[14] Bell SJ, William AB, Wiesel P, Wilkinson K, Cohen RC, Kamm MA. The clinical course of fistulating Crohn's disease. Aliment Pharmacol Ther 2003;17:1145-1151.

[15] Van Assche G, Dignass A, Reinisch W, van der Woude J, Sturm A, de Vos M, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disesae: special situations. J Crohns Colitis 2010;4:63-101.
[16] Buchanan GN, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CR. Clinical examination, endosonography, and MR imaging in preoperative assessment of filstula in ano: comparison with outcome-based reference standard. Radiology 2004;233:674-681.
[17] Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr; 106(4):661-73. Epub 2011 Mar 15.
[18] Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn's disease. A meta-analysis. Ann Intern Med 1995; 122:132–142.
[19] Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340:1398–1405.
[20] Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350:876–885.
[21] Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009;58:940-948.
[22] Vavricka SR, Schoepfer AM, Bansky G, Binek J, Felley C, Geyer M, Manz M, Rogler G, de Saussure P, Sauter B, Scharl M, Seibold F, Straumann A, Michetti P; Swiss IBDnet. Efficacy and safety of certolizumab pegol in an unselected crohn's disease population: 26-week data of the FACTS II survey. Inflamm Bowel Dis. 2011 Jul;17(7):1530-1539.
[23] Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther 1995; 9:293-300.
[24] Marshall JK, Irvine EJ. Rectal corticosteroids vs alternative treatment in ulcerative colitis: a meta-analysis. Gut 1997; 40: 775-781.
[25] Travis SPL, Stange EF, Lemann M, Oresland T, Bemelman WA, Chowers Y, Colombel JF, D'Haens G, Ghosh S, Marteau P, Kruis W, Mortensen NJMcC, Penninckx F, Gassull M. European evidence-based consensus on the management of ulcerative colitis: current management. J Crohn Colitis 2008;2:24-62.
[26] Mulder CJJ, Fockens P, Meijer JWR, et al. Beclomethasone dipropionate (3mg) vs 5-aminosalicylic acid (2g) vs the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. Eur J Gastroenterol Hepatol 1996; 8: 549-553.
[27] Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006; 2: CD000543.
[28] Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2006;19: CD000544.
[29] Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut 2005; 54:960-965.
[30] Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2007; 24: CD000478